## Mutation

A mutation is a heritable change in the base sequence of the nucleic acid in the genome of an organism. strain carrying such a change is called a mutant. A mutant by definition differs from its parental strain in genotype, the nucleotide sequence of the genome.. Some mutations have benefit (new or enhanced activity ,this drives evolution). Some mutations harmful (cause decreased activity or loss of activity).

Although some of these mutations are lethal or cause serious disease, many have minor effects as they do not result in residue changes that have significant effect on the structure and function of the proteins. Many mutations are silent mutations, causing no visible effects at all, either because they occur in non-coding or non-functional sequences, or they do not change the amino-acid sequence due to the redundancy of codons.

## Mutagens

Mutagen is a physical or chemical or biological origin agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level. As many mutations can cause cancer, mutagens are therefore also likely to be carcinogens. Not all mutations are caused by mutagens: so-called "spontaneous mutations" occur due to spontaneous hydrolysis, errors in DNA replication, repair and recombination.

Mutagens cause changes to the DNA that can affect the transcription and replication of the DNA, which in severe cases can lead to cell death. The mutagen produces mutations in the DNA, and deleterious mutation can result in aberrant, impaired or loss of function for a particular gene, and accumulation of mutations may lead to cancer.

Mutagens may act directly on the DNA, causing direct damage to the DNA, and most often result in replication error. Some however may act on the replication mechanism and chromosomal partition. Many mutagens are not mutagenic by themselves, but can form mutagenic metabolites through cellular processes. Such mutagens are called promutagens.

## Types of mutagens

## Physical mutagens:

- Ionizing radiations such as X-rays, gamma rays and alpha particles create ions and free radicals that break molecular bonds and damages DNA Nonionizing radiation (Ultraviolet radiations) with wavelength above 260 nm are absorbed strongly by bases, producing pyrimidine dimers, which can cause error in replication if left uncorrected.

- Radioactive decay, such as 14C in DNA which decays into nitrogen.

## Chemical mutagens

A large number of chemicals may interact directly with DNA.

- Reactive oxygen species (ROS) – These may be superoxide, hydroxyl radicals and hydrogen peroxide,

- Deaminating agents, for example nitrous acid which can cause transition mutations by converting cytosine to uracil.

- Polycyclic aromatic hydrocarbon (PAH), when activated to diol-epoxides can bind to DNA and form adducts.

- Alkylating agents such as ethylnitrosourea. The compounds transfer methyl or ethyl group to bases or the backbone phosphate groups. Guanine when alkylated may be mispaired with thymine. Some may cause DNA crosslinking and breakages. Nitrosamines are an important group of mutagens found in tobacco, and may also be formed in smoked meats and fish via the interaction of amines in food with nitrites added as preservatives. Other alkylating agents include mustard gas and vinyl chloride.

- Aromatic amines and amides have been associated with carcinogenesis since 1895 .

- Alkaloid from plants, such as those from Vinca species may be converted by metabolic processes into the active mutagen or carcinogen.

- Bromine and some compounds that contain bromine in their chemical structure.

- Sodium azide, an azide salt that is a common reagent in organic synthesis and a component in many car airbag systems

- Psoralen combined with ultraviolet radiation causes DNA cross-linking and hence chromosome breakage.

- Benzene, an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber and dyes.

## Base analogs

- Base analog, which are in structur with similar bases and bonded to DNA by error between thymine and adenine which can substitute for DNA bases during replication and cause transition mutations.

### Intercalating agents

- Intercalating agents, such as ethidium bromide and proflavine, are molecules that may insert between bases in DNA, causing frameshift mutation during

replication. Some such as daunorubicin may block transcription and replication, making them highly toxic to proliferating cells.

### Metals

Many metals, such as arsenic, cadmium, chromium, nickel and their compounds may be mutagenic, they may however act via a number of different mechanisms.

## Biological agents

• **Transposon**, a section of DNA that undergoes autonomous fragment relocation/multiplication. Its insertion into chromosomal DNA disrupt functional elements of the genes. Transposons have the ability to move (transpose) from one site to another.

Elements known as **Insertion Sequences (IS)** have a specific ability to insert into other DNA sequences, thus generating insertion mutations. A substantial proportion of spontaneous mutations may be due to inactivation of genes by insertion of a copy of an IS element rather than by replication errors.

• **Virus** , Virus DNA may be inserted into the genome and disrupts genetic function. Infectious agents have been suggested to cause cancer as early as 1908 by Vilhelm Ellermann and Oluf Bang.

**Mutagens can be divided into Three classes based on the ways they cause mutation:**

**1- Base analogs. Examples:** ( 2-aminopurine, ) (5-bromouracil.) These base analogs are incorporated into DNA where they mispair with other bases. 5BU can pair with adenine and guanine. These result in transition mutations.

**2- Base** modifications causing mispairs Examples: ethyl methane sulfonate (EMS). These mutagens modify bases on DNA such that they mispair. EMS alkylate the O6 of guanine, which is highly mutagenic and causes mispairing with thymine ,and show preference for GC to AT transitions. However, they also alkylate bases at many positions with other effects. Nitrous acid and hydroxylamine deaminate cytosine to yield uracil (see deamination above) resulting in transition mutations.

**3- Base modifications which destroy pairing:** SOS-dependent mutagens. Examples: UV light, benzo(a)pyrene, aflatoxin B1 (i.e. most carcinogens) These mutagens or their metabolites modify DNA so that no specific pairing is possible; replication cannot proceed past the lesion. Unrepaired AP sites also elicit this response.